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ABSTRACT

Malaria, the greatest pandemia in the world, claims an estimated one million lives each year in Africa alone. While it may still be said that for the most part malaria is found in what is known as the world's poverty belt, cases are now frequently diagnosed in western countries. Due to resistant strains of malaria which have developed because of exposure to drugs and insecticides, the incidence of the disease is rising substantially throughout the world. The development of strains resistant to drugs in humans beings has put an end to previously effective treatment strategies. Mosquito resistance to DDT and the other organochlorines and organophosphorus compounds put an end to a one-sided campaign to eradicate malaria. This journal issue provides up-to-date information on the disease and guidelines for therapeutic interventions. An editorial and introduction establish contexts for discussions of epidemiology, immunity, clinical signs, antimalarial drugs, drug resistance, prophylaxis, and treatment. Concluding remarks focus on prospects for controlling the disease in the future. Resources for further reading are listed. (RH)

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CHILDREN IN THE TROPICS

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MALARIA

1989 - N° 178

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ICC soon turned essentially toward Third World children and devoted its activities to the training and education of personnel with social, educational and administrative responsabilities as well as medical and paramedical workers. The desire for greater efficiency has led it to work increasingly with trainers and to concentrate its efforts on the methodological and educational aspects of mother and child care programmes.

JCC is also engaged in an attempt to further study — and — action on some aspects of the life and health of children and their family, so as to contribute to practical improvement, particularly in the fields of growth, nutrition, planned parenthood, the control of transmissible and nutritional diseases, preschool and school education, the needs of disabled and underprivileged children, etc.

Over this period of more than 30 years, a large amount of documents on children and adolescents, mostly from the developing countries, has been accumulated. This international documentation has been classified and sorted out, and has been computerized since 1983 : a bibliographic data base (BIRD : « Base d'Informations Robert Debré ») may be consulted anywhere in the world, through international communications networks. ICC also publishes periodicals, educational documents and specialized bibliographic bulletins.

As for its legal status, the International Children's Centre is a foundation under french law of recognized public utility, administered by an executive board with broad international membership.

1989 - N° 178

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edited by

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EDITORIAL

by M. LARIVIERE

The worldwide incidence of malaria is estimated by WHO at 100 million cases each year. According to D. Stürchler (Parasitology Today, 1989, vol. 5, n 2, p. 39-40), the figure furnished by the international organization should be multiplied by five, to provide an adequate picture of the actual situation. On the basis of data for 1986, he reaches an estimation of 489 million clinical cases, of which 243 million were caused by **Plasmodium falciparum**, resulting in at least 2.3 million deaths.

It is not my intention to take part in a debate on statistical methodology. Its very existence is proof in itself of our difficulty in understanding and controlling this endemic parasitosis, despite the fact that it has been known since ancient times, and that in 1957 some "experts" predicted its possible eradication, perhaps even within a short period of time.

The correlary of that illusion is the utter confusion experienced at present, in the face of the rapid extension of resistance to drugs combatting Plasmodium falciparum malaria, caused by the most fearsome of all human haematozoan parasites. Following the senseless dream of total vector destruction by the spraying of insecticides, chemoprophylaxis was given free rein, generating all sorts of laxist behaviour, including the prescription of insufficient doses of drugs, which unquestionably prepared the ground for the selection of drug-resistant strains.

The history of malaria is a series of ups and downs, of hopes raised by prodigious discoveries and dramatic failures, generated by the reckless pretentions of mankind when it disregards and defies the specific laws of the natural environment.

By 1630, "swamp fever" was already considered a distinct form of intermittent fever.

In that year, the Jesuit Don Francisco Lopez, who was travelling in Peru, taught the Indians the curative value of cinchona bark, which he himself successfully used to cure the Italian Cardinal Juan Di Luigi in 1632. From then on, people in those parts of Europe where malaria was endemic (Italy, France, Holland, etc) were prepared to pay fortunes for "Cardinal's powder" or Jesuit's bark", since it was very difficult to obtain.

It took another two centuries for science to replace empiricism.

The first fundamental discovery was made in 1620 by two French pharmacists, Pelletier and Caventou, who isolated alkaloids of the cinchona bark, or **Quinine,** which still remains the best active drug available today for the most urgent malarial condition : for the treatment of pernicious attacks. So, while some fanciful speculations are still being heard as to the actiology and transmission of malaria, we actually have at our disposal an active drug and the means of diffusing it. In 1830, Maillot used it successfully to treat soldiers fighting to conquer Algeria.

But the most important discovery was made by A. Laveran, a French military physician in Algeria. In 1878 in Bone, and again in 1880 in Constantine, he demonstrated the

existence of parasites in the red blood cells of patients, and described the different biological stages of the three most widespread species. In 1889 the Italian Golgi established the chronology order of the **schizogony cycle.**

By that time, then, the aetiological agents of clinical malarial manifestations are known, as well as the treatment capable of eliminating them. The regular ingestion of quinine in areas where malaria is endemic was also observed to prevent the development of parasites in the blood, and of fever cases, leading to the idea of prevention through chemoprophylaxis, subsequently put into practice. The spectre of malaria no longer seemed to haunt the colonial adventure : there was quinine, necessarily taken along to prevent or cure an illness that was now identified, although nothing was yet known of the ways in which it enters the body.

Quinine was universally available. Its use for chemoprophylaxis was found to be extremely unpleasant and demanding, since it called for strong self-discipline with the twice-daily ingestion of bitter pills, and frequently induced unacceptable side effects. Many people preferred to wait until they experienced the prodromes of a fever paroxysm before taking it. As a result, intermittent chemoprophylaxis at the most unorthodox doses, with frequent abuse of excessive doses to ward off the first clinical manifestations paved the road for **Bilious Haemoglobinuric Fever,** or "black-water fever", the first setback to be caused by uncontrollable self-medication.

At long last the secret of contamination was unveiled. In 1895 the physician R. Ross, a major in the Army of India, conceived the idea of a sporogonic cycle for **human plasmodia** in the "spotted wing" mosquitoes (the Anopheles), and established the complete cycle of an avian plasmodium in **Culex fatigans.**

In 1898, on the basis of Ross' work, the Italian researchers Grassi, Bastianelli and Bignami definitely established the biological cycle of human plasmodia in the different anopheline species.

There was reason to believe at the time that the wheel had come full circle : a person infected by an anopheline bite might in turn infect a mosquito. This would explain continual transmission under natural circumstances.

It is a fact, however, that nothing is ever final in biology.

The discovery of the man-mosquito cycle put an end to the mystery and cleared the way for further discoveries, but it also led to other excessive and occasionally catastrophic attempts at prophylaxis. The discovery of the vector role played by anophelines triggered an enormous number of entomological research projects aimed at inventorying definite or putative vector species, and describing their biological characteristics and behaviour. Larva control actions, more feasible than the control of adults, were developed in many regions. Some, including the Rome campaign and others aimed at certain limited foci, were highly successful, while others were terrible failures, and gave rise to catastrophic epidemics.

On the eve of the second world war, global malarious endemicity was still very high, and mosquitoes continued to harry mankind as they had for some 100 million years. Only the privileged benefitted from a degree of protection, since they could sleep under mosquito netting or use insect repellents (including slow-burning pyrethrum-saturated "mosquito coils", essence of citronella rubbed on the skin, etc) to ward off mosquitoes, who usually bite at night, and had access to quinine for prophylactic and therapeutic use.

At the same time, an extremely high infantile mortality rate continued to be the price paid by indigenous populations of endemic areas for their naturally acquired **immunity.**

With the end of World War II and its attendant illusion of peace came the illusion that it would now be possible to overcome malaria.

Biochemical and pharmacological research begun long before the war then produced the first generation of synthetic antimalarials, of which **chloroquine** (NIVAQUINE®) was clearly the most remarkable and least expensive.

The commercialization of DDT, a powerful insecticide, gave new impetus to mosquito control. Its use as a larvicide, and/or in spray form, in homes, to destroy adult mosquitoes, had interrupted transmission in some limited foci.

In 1957, encouraged by these successful attempts, WHO decided to engage in a worldwide battle, based on the use of insecticides, with the **eradication** of malaria as its objective. This decision was actually in complete defiance of the basic understanding already acquired by malariologists, and failed to recognize the cultural, social and economic diversity of situations around the world.

Action that is feasible in one region is not necessarily applicable in another. The anopheline vector species are not the same everywhere, nor do they possess identical biological characteristics. The nyctohemeral (night and day) activity of adults, their resting place after the blood-meal, their larval habitats all show considerable inter-species variations.

Human population groups also differ, and unavoidably, the operational implementation of this policy was extremely heterogeneous.

The inability to effectively reach all of the major endemic areas, as well as the discovery of the first cases of **anopheline resistance** to DDT, and subsequently to the other organochlorines and organophosphorus compounds put an end to this pretentious ambition. The problem was then to head off the development of generalized resistance : to do so, it was decided that insect control would be combined with an extensive **mass chemotherapy** programme based on the administration of chloroquine.

All sorts of solutions were invented to ensure the broadest possible population coverage by this drug : administration might be continuous, to all age groups, intermittent in areas where transmission is seasonal, limited to at-risk groups (pregnant women, children), passive, through the incorporation of chloroquine in table salt (this was known as Pinotti's method, and was first experimented in Latin America), or based on user "participation" (collaboration of pharmacists or village leaders, etc).

Strangely enough, whereas chloroquine chemoprophylaxis had previously proved effective and well tolerated at the dose of 600 milligrams weekly for adults, the instructions issued by the international experts, most of whom were from English-speaking countries, then called for a reduction to 300 milligrams.

Another frenzy of anarchic self-medication then unfurled around the world, where the numerous "generic" drugs on the market - chloroquine tablets produced just about anywhere, and therefore defying surveillance - contributed to insufficient drug dosage.

In 1959, the first cases of **Plasmodium Falciparum resistance to chloroquine** were reported in Colombia, where Pinotti's method had been applied. From there it spread to

tropical America, then to Asia during the 1960's. It reached the English-speaking eastern African countries in 1974, and subsequently spread to central and western Africa.

Drug resistance put an end to earlier strategies, since they had no substitute drug on which to rely. **Multidrug resistance** affects extensive areas, especially in South-East Asia where even quinine is less effective, and in some cases totally inactive.

Attempts to curb this evolution through the use of drug combinations met with varying success in different countries. Some antibiotics, whose schizonticidal activity had been known for years but had been neglected because of the remarkable efficacy of chloroquine, again became relevant. Funds were poured into research on vaccines, but no breakthrough was in sight. The pharmaceutical industry went to work on the development of new molecules : Mefloquine (LARIAM®) and Halofantrine (HALFAN®) had already been commercialized, while Artemisine and Quinghaosu were still in the laboratories.

Are we now searching for another "Cardinal's powder" again ? The answer is no, for substantial ground has been gained once and for all. Much is now known, and the constant, fantastic advances in scientific technology give us every reason to hope.

Of the lessons to be drawn from the past, we should retain the patient efforts, and refrain from crudely and thoughtlessly brandishing any powerful new weapon as soon as it is devised, with complete disregard for our environment. But above all, we should first honestly determine what is feasible, avoiding all demagoguery, and act only when assured of the continuity of our enterprises. 100,000 lives were taken in a recent epidemic of malaria affecting the High Plateaus of Madagascar. And yet, the disease seemed to have been eliminated, following a long battle using insecticides and mass chemoprophylaxis in children, with its inevitable corollary, a serious decrease in immunity among the inhabitants.

But the programme had not been extended to the rest of the country, so that transmission continued actively in the areas bordering on this "privileged" region. Over the past fifteen years, the economic situation in this large Indian Ocean island had degenerated to the point that the malaria control efforts concentrated in the High Plateaus could no longer be financed, and were therefore discontinued. The ensuing catastrophe was unavoidable : infected anophelines coming from neighbouring areas invaded the High Plateaus, where a low level of naturally acquired immunity prevailed within the population, producing the ideal conditions for a fatal, epidemic explosion.

Should we give up, then ? To do so would be no wiser than to act hastily and thoughtlessly.

The eradication of malaria in the short or middling term is a myth, but it remains an objective toward which to work, patiently, by sustained, gradual efforts. To achieve lasting success, such action must be consistent with the economic and social perspectives of the populations of those areas where malaria is endemic, and contribute to the broadening of those perspectives.

Paradoxically, the present alarming situation is perceived essentially by the "privileged" Europeans and Americans, who fear that extensive drug resistance may cause some prejudice to their business ventures or holiday travels. How timorous of them, when they have the choice, in the first place, of attempting the venture or not, and if they do, they have access to the latest preventive drugs, and then again to the comfort of air-conditioned hotels.

In the "brush" of Africa, Asia and tropical America, people continue to experience malaria as a fatality.

Such fatalism is unacceptable of course, but this attitude, a mixture of patience and of incredulity in the face of what these people know to be short-lived, vain agitation constitutes a strong, pragmatic openness.

The chemical control of anophelines and mass chemoprophylaxis have now come up against almost unsurmountable obstacles. What remains is the immunity acquired by inhabitants in permanent contact with the pathogenic environment. This must be preserved, while reducing to a minimum the price that has always been paid for it : high infantile mortality.

As some recent communications have stressed, the reduction of the number of infecting bites may depend on the generalized use, in homes, of mosquito nets with or without insecticide spray.

Above all, there is an urgent need to develop and extend basic health centres or community services, and to equip them with microscopes so that they may diagnose and treat severe attacks of malaria. Those antimalarial drugs the most active treatment available be implemented.

The development of naturally acquired immunity must be encouraged, but without the dramatic price paid for its acquisition.

INTRODUCTION

From time immemorial, malaria has always been one of the most widespread human diseases, affecting the inhabitants of tropical climates, in particular, but also active in temporate areas in former times. It is also one of the oldest diseases. It is mentioned in the earliest Egyptian, Indian and Chinese writings, and its clinical symptoms were described by Hippocrates 400 years before the Christian era.

The word MALARIA clearly expresses the context in which the disease is seen, since it is derived from the Italian "mal aria", or BAD AIR, suggesting the exhalations of marshlands.

PALUDISME, the French term, is derived from the Latin Palus, meaning MARSH. Malaria, then, is marshland fever, related to the proliferation of its vector, the mosquito, in those swampy regions.

Until the last few years, few questions were raised concerning the clinical, epidemiological, therapeutic or entomological aspects of our knowledge of malaria.

In fact, a degree of self-confident routine had set in, when, all of a sudden, like a thunderbolt in the otherwise serene skies of the tropics, serious problems developed : drug resistance and resistance to insecticides, with their fatal consequences both in malaria-infested countries and in Europe, galvanized workers and gave new impetus both to this anciently known disease and to efforts to control it.

It is this NEW IMPETUS, and these new developments, that will be discussed here, with neither optimism nor pessimism, but realistically. It should be clear that while the Plasmodium is still transmitted by a mosquito, everything else pertaining to it is changing, and being modified, and that today's truths may be tomorrow's falsehoods. It is wise, then, to think within the boundaries of the present, with no assurance of what the future holds in store.

What is the current situation ?

In every aspect of the question, unexpected, surprising and now terribly disturbing problems have arisen :

The treatment of malaria requires easy-to-use, reliable products that are effective against resistant strains in those areas where these are present. The rapid extension of drug resistance raises the question of the efficacy of the treatments currently implemented, and we are running out of therapeutic weapons. Much attention seems to be focussed on the development of a vaccine, despite the complexity of the immune mechanisms generated by plasmodial infection.

Vector control faces :

— technical difficulties : resistance to insecticides ;
— economic difficulties : high cost of insecticides and difficulty in organizing regular, consistent insect eradication campaigns ;
— ecological dificulties : danger of residual insecticides ;
— ethological difficulties : modifications in the behaviour of vectors, which are already circumventing control schemes.

EPIDEMIOLOGY

Malaria is the greatest pandemia in the world : one BILLION individuals are exposed to it. Mortality is substantial : in black Africa, it takes an estimated one million lives each year. Work incapacitation caused by malaria is quite serious, since the disease is most virulent during the heavy farming season.

The disease affects people with no regard for age or sex, but pregnant women and children are more sensitive than other population groups to the effects of the disease.

Even if an expectant mother has developed a degree of naturally acquired immunity before her pregnancy, she is temporarily deprived of protection at that time, and may easily have attacks of malaria caused by parasites of which she was a carrier before her pregnancy. Reactivation or a relapse of the disease may therefore be observed in the absence of any mosquito bite.

The risk of malaria is greatest during women's first pregnancy and then especially during the last three months of gestation.

Malaria, and Falciparum malaria in particular, takes a most severe form during pregnancy, possibly resulting in miscarriage or premature delivery. It also causes retarded intrauterine growth and neonatal malaria.

The presence of these parasites in an organism already infested with many other parasites has a catastrophic effect on children's physical growth and psychomotor development. Further, it mobilizes the body's defenses, otherwise needed to fight off other diseases such as measles.

To summarize, the frequency of the disease is rising substantially throughout the world, making the situation increasingly dramatic.

WHAT IS MALARIA ?

Malaria is a parasitic disease caused by the introduction and reproduction within the human body of a sanguicolous protozoan of the genus plasmodium, transmitted by a mosquito (the vector), the female Anopheles.

The epidemiological cycle of malaria has not changed with time ; at most, some new knowledge of the exoerythrocytic phase has been gained, as will be seen below.

The vector

The Anopheles are haematophagic mosquitoes ; like all insects, they require blood for the maturation of the fertilized eggs within the females.

When at rest, anophelines do not take the same pose as other mosquitoes ; adult anophelines stand obliquely in relation to the plane on which they rest, while other mosquitoes retain a parallel position. There are also some distinguishing morphological

features : differing mouthpieces enable the female to absorb mammal blood, while the male may suck plant juices. Heat and humidity condition the activation of their reproductive cycle :

— in temperate areas, anophelines only lay eggs during the warm season ;
— in equatorial areas, where hot, humid conditions constantly prevail, they are always active ;
— in tropical areas, their activity peaks during the rainy season and generally ceases during the dry season.

It is therefore most important to elucidate the biological functioning of females : this knowledge has greatly contributed to the development of vector control. Anophelines generally bite in the evening or early in the night, but :

— there are major inter-species variations ;

— mosquitoes have adjusted to the habitual spraying of insecticides on the inner walls of dwellings by changing their behaviour : where they formerly tended to bite inside homes (endophagic species), some now bite outdoors (exophagic species), since they cannot rest on insecticide-coated walls.

Some species have very narrow food preferences, while others are less demanding. The anthropophilic species feed exclusively on human blood, and are therefore the most dangerous for the transmission of malaria ; the zoophilic species prefer animal blood ; others are attracted to both (anthropozoophilic). Last, some are able to adjust to any situation, and are said to be adaptable.

Following their blood-meal, the females seek out a resting place where they may digest and allow the eggs within them to develop. In hot, humid tropical areas there is a period of about 48 hours between the ingestion of blood and ovipositioning. At the end of this cycle, the female finds an oviposition site in which to place her eggs (stagnant surface water : marigot, stored water, gutter, etc). The eggs then develop into larva, which become nymphs, and these in turn are transformed into winged adults (imagos), two to three weeks after the eggs are laid, under optimal conditions.

Two hosts are required for the entire cycle to occur :

— man : considered to be the only viral reservoir ;
— anophelines : vectors, intermediate hosts.

The following four plasmodial species parasite human beings :

— plasmodium falciparum ;
— plasmodium vivax ;
— plasmodium malariae ;
— plasmodium ovale.

These are intracellular protozoans. They are also known as haematozoans, since they parasite the red blood cells, or erythrocytes, and develop through :

— asexual reproduction in man ;
— sexual reproduction in mosquitoes.

Life cycle

During their biological life cycle, the size and appearance of plasmodia change constantly, as they go through alternating stages of growth and division.

Human beings are infested when they are bitten by a female anopheline which inoculates parasites in the form of microscopic unicellular elements, or sporozoites. Following a brief stay in the blood, where they are not transformed, the sporozoites travel to the liver cells, invade these, and replicate. Sporozoites undergo several divisions, leading to the formation of schizonts, which completely pack all parasite-ridden liver cells. These rupture, releasing large quantities of merozoites into the blood stream. The merozoites will then invade the erythrocytes, and continue to multiply.

Within the erythrocytes, the merozoites go through several stages ; first trophozoites, then schizonts and finally mature schizonts that burst, destroying the red cells and releasing the merozoites. The latter may then invade other red cells or be transformed into potentially sexual elements, the male or female gametocytes which may then be sucked up by anophelines. The process of transmission can only continue if this actually occurs.

Within the anopheline, the gametocytes develop into male or female gametes. The male gametes fertilize the female gametes, thus producing an oocyst. The sporozoites released by the oocyst then accumulate in the insect's salivary glands, and are deposited at the site of the mosquito bite.

One important point should be kept in mind : since the sporozoites are stored in the insect's salivary glands, they are not all injected in a single bite, and an anopheline may contaminate several individuals in the course of its life.

The idea that secondary hepatic forms caused by some types of plasmodium may cause relapses seems to have been abandoned.

Merozoites produced by the bursting of intraerythrocytic schizonts were claimed to reinvade the hepatocytes. This hypothesis of a secondary reinvasion is now seriously questioned, while there are many indications of the existence of a latent (hepatic) tissue stage. These plasmodial cells are called hypnozoites, or dormozoites, and most certainly exist in Plasmodium vivax and Plasmodium ovale.

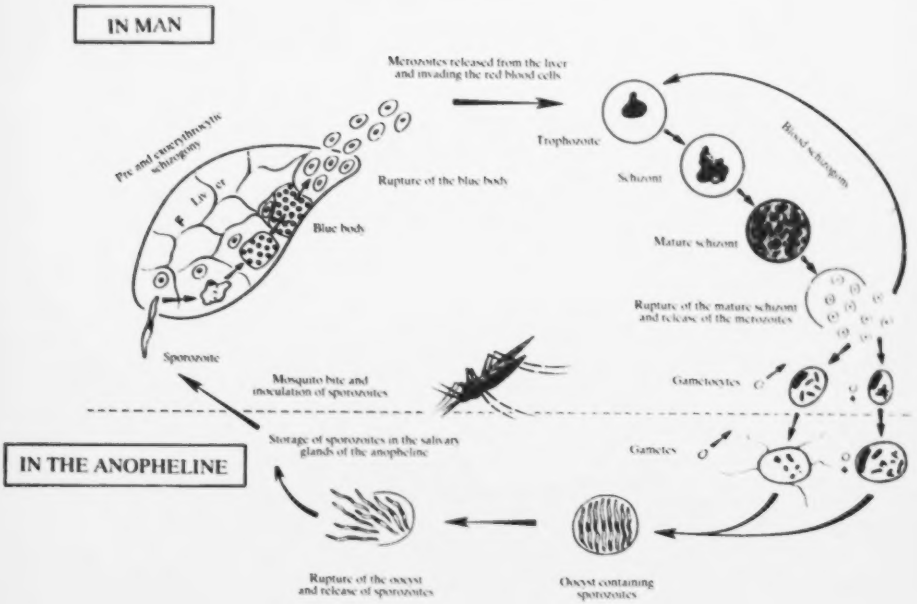
In the case of Plasmodium malariae, some recent findings seem to indicate the possibility, in some cases, of recrudescence caused by erythrocytic forms remaining within the organism for considerable periods of time.

Plasmodial species

Plasmodium falciparum

This is the worst species, the lethal species. A temperature of more than 18 °C is required for the mosquito to accomplish its life cycle ; it is therefore the most prevalent species in the hot, humid intertropical zone.

Figure 1 - Life cycle of plasmodia



Source : LARIVIERE M. Parasitologie tropicale. Les grandes endémies - Epidémiologie - Prophylaxie. Editions Foucher, Paris. 1978.

The life cycle lasts 7 to 15 days, with no possible recrudescence. The erythrocytic forms frequently persist for 2 months. In individuals with no prior immunity and choroquine-resistant malaria, some bouts of fever caused by Plasmodium falciparum have been observed as late as 6 months after leaving the endemic area.

Parasite reproduction occurs essentially in the deep cerebral or renal capillaries, whence the severe clinical repercussions in cerebral malaria, or pernicious attacks.

Plasmodium vivax

The habitat of this widely prevalent plasmodial species extends from the lattitude of 37 North to 25 South. Its life cycle may last from two weeks to 9 months.

Parasitaemia is rarely intense (scarcely more than 2 % of red cells are parasited). The erythrocytic cycle lasts 48 hours ; this explains the three-day rhythm of intermittent paroxysms.

Plasmodium malariae

This species has a scattered habitat.

Tissue forms may live for 3 years or more (occasionally for over 20 years). The erythrocytic cycle lasts 72 hours, causing the four-day rhythm of intermittent paroxysms.

Plasmodium ovale

Quite similar to Plasmodium vivax, with which it was confused for many years, it replaces P. vivax in those areas from which the latter is absent (Black Africa).

It lives for several months. The erythrocytic cycle lasts 48 hours.

Infestation with several species, or multiparasitism, is frequent.

ENDEMIC MALARIA

It is closely dependent upon the local climate, which influences the ecology of mosquitoes. This in turn determines disease conditions.

Areas are defined as holo-endemic, meso-endemic or hyper-endemic, according to the extent of the malaria problem.

In the hot, humid equatorial areas, anophelines find ideal conditions in which to lay eggs : stagnant surface waters, humidity, water collecting in tree hollows, palm leaves and other hollow objects make ideal larval habitats for mosquitoes. Since these conditions remain stable throughout the year, transmission is continuous.

In savannah areas, the number of oviposition sites is multiplied when the rains begin : seasonal epidemics occur against a background of ongoing transmission.

In Sahelian areas, where the rainy seasons last two to three months - when they occur - malaria is said to be occasional.

Last, in some regions such as the high plateaus of eastern and southern Africa, transmission ceases completely during the dry, cold season : malaria is said to be sporadic.

Geographical distribution

While it may still be said that malaria problems mostly prevail in what is known as the world's poverty belt, cases are now frequently diagnosed in western countries.

In Africa, malaria is rampant everywhere. It is widespread in intertropical Africa, in the savannah regions, in the Sahel, on the high plateaus of eastern and southern Africa. It also takes the form of small seasonal epidemics in some saharan oases. It is highly prevalent in Madagascar and the Comoros. In Mauritius, where eradication had been successful, malaria is once again endemic owing to the relaxing of control measures. The disease is apparently no longer endemic on Reunion Island.

In Asia, foci are quite widespread, affecting Thailand, Cambodia, Viet Nam, Burma, China, the Indian peninsula and Asia Minor.

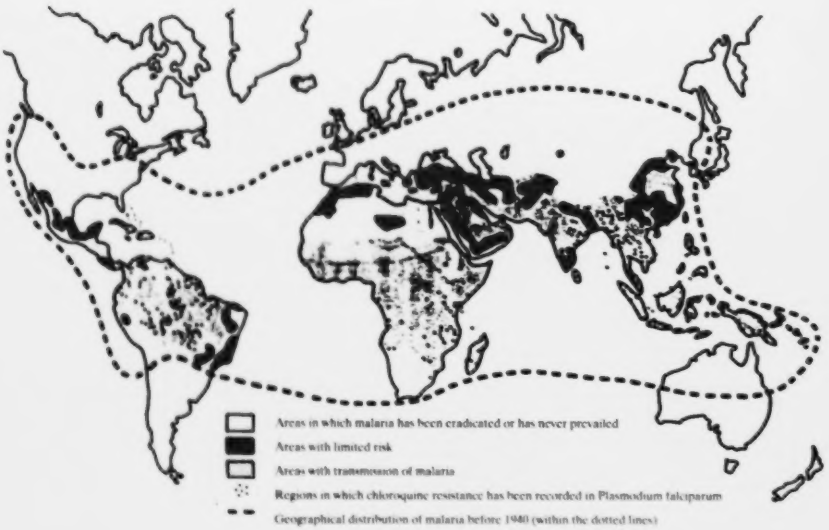
There is no malaria in North America. By contrast, it prevails under all of the tropical and equatorial climates of Central or South America, but the high mountains and coastal plains have been spared. Malaria is absent in the French Antilles, but does exist on some islands such as Haiti.

In Oceania, some islands, such as Papua New Guinea and the Solomon Islands are affected, while others - Tahiti, New Caledonia, the Loyalty Islands - have been totally spared. Some foci exist in the north-eastern part of Australia.

In Europe, malaria has been eradicated, and has disappeared from the marshy regions in which it formerly prevailed. Only the names of some towns or villages (La Palud, etc) are still suggestive of it. A new problem has arisen, however, with the importation of malaria ; the increasingly frequent and far-reaching population mobility, for personal, professional or political reasons, explain the cases of malaria observed in Europe.

The reported cases of indigenous malaria (anophelines transported in airplane cabins) are exceptions. Transfusion malaria is prevented by routine antimalarial serological testing of donor blood.

Figure 2
Map of malarial epidemiology


Areas in which malaria has been eradicated or has never prevailed
Areas with limited risk
Areas with transmission of malaria
Regions in which chloroquine resistance has been recorded in Plasmodium falciparum
Geographical distribution of malaria before 1940 (within the dotted lines)

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IMMUNITY

A classical description of clinical signs of malaria has long been in existence, but the development of chloroquine resistance and the increased number of cases of the disease in persons who are not natives of endemic areas have provided new insight into their pathogenesis.

Only the erythrocytic stage causes clinical manifestations of malaria. Other co-factors are involved :

— extent of naturally acquired individual immunity to the disease (formerly called premunition) ;
— the specific plasmodial species (only Plasmodium falciparum is responsible for fatal cases of malaria) ;
— last, the degree of resistance of the specific plasmodial strain to the drug delivered preventively or for first-line treatment.

There is no such thing as natural inborn protection against malaria. However, people living in an endemic area and who are repeatedly re-infected may develop an immunity known as naturally acquired immunity, which is of relatively long duration.

An individual with the latter type of protection is a carrier of a number of circulating haematozoans inferior to the threshold at which clinical manifestations occur. This state may only be maintained by the reintroduction in the blood stream of a sufficient number of haematozoans, through regularly repeated bites by infected anophelines. As contacts with the same antigen are repeated, the body reacts with an increasingly rapid and substantial production of specific antibodies, since the immune system "remembers". These antibodies then neutralize the parasites, by reacting with the antigens.

Another defense mechanism is based on cell-mediated immunity : cells specialized in the defense of the organism work at eliminating the parasites.

As soon as this "supply" ceases, the state of naturally acquired immunity declines, and may even disappear completely : it is said to be unstable.

A certain type of genetically determined natural protection against malaria does seem to exist ; it affects healthy carriers of sickle cell anaemia (haemoglobin S), and individuals with glucose-6-phosphate dehydrogenase (G-6-PD), and prevents the development of the parasite in the red blood cells.

Naturally acquired immunity may be transmitted by a mother to her child through the maternal antibodies : the child is protected during the first 4 to 6 months of life, but beyond that period any infection exposes him or her to a very serious risk, and urgently requires treatment.

Two distinct categories of individuals susceptible of developing a malarious infection have been defined :

— non-immune individuals who are not protected against this infection either because they have not acquired immunity or because they have lost it. Typical of this category is the traveller from a Western country, who visits an endemic area for pleasure or business

reasons. Another example is the case of migrant workers who spend some years in the West and return home on a holiday. The small child who is no longer protected by his or her mother's antibodies and whose body must then produce its own antibodies, builds up immunity through repeated episodes of malaria, provided none of these are so severe as to cause the child's death. It is a fact that most fatal cases of malaria occur between the ages of 6 months and 5 years. The extremely high mortality rate for small children in endemic regions is explained by the length of time and large number of bites required for the acquisition of partial immunity. This is particularly true in Africa, where an estimated one million children under 5 years of age die of malaria ;

— the second category is represented by semi-immune or immune individuals. The term of semi-immune is preferred, since such immunity is neither total nor definitive. This is the case of individuals living in endemic areas. Constant exposure to malaria parasites gradually induces partial immunity. This may require up to 5 years, depending on the frequency of bites by infecting mosquitoes. The number of bites by infected mosquitoes required for the acquisition of partial immunity is estimated at 40 to 50, although each infecting bite does not result in an acute attack of malaria. Partial immunity does not prevent the development of the disease, it works toward limiting parasitaemia and develops physiological tolerance, thanks to which parasitaemia no longer produces severe symptoms.

Drug treatment is enhanced by this state of partial immunity, since such patients may more easily be protected or cured than those with no previous exposure to the parasite.

In recent years, during the drought in Sahelian Africa, endemic malarious areas witnessed the disappearance of their mosquito vectors, since no larval habitats were available. Their normally semi-immune population then became non-immune, and infantile mortality was considerable when it finally did rain.

Another type of situation is observed in the high plateaus of southern Africa, where malaria is so seasonal that from one year to the next people's immune status often declines to a level quite similar to that of true non-immune individuals.

CLINICAL SIGNS

They are defined as uncomplicated attacks, complicated attacks and visceral malaria. Each of these must be discussed in specific relation to the plasmodial species involved.

PLASMODIUM FALCIPARUM

Incubation generally lasts 5 to 7 days. At the end of this period, the merozoites contained in the intrahepatic schizonts break out and invade the red cells. Endoerythrocytic schizogony follows a well-defined pattern, but there is never any recrudescence after spontaneous termination or effective treatment.

Attacks are termed "uncomplicated" or "pernicious" depending on the intensity of parasitaemia and the contribution of the individual's immune defenses (cf. naturally acquired immunity).

Uncomplicated attacks

It is imperative to keep in mind that an uncomplicated attack may develop into a complicated attack at any moment, particularly at the present time, with the current problem of drug resistance. Consequently, any fever occurring in an endemic malarious area, even in a patient claiming to be under proper prophylactic treatment should be viewed as a case of malaria until proof to the contrary has been formally established.

The main sign of malaria is high fever, 39 °C - 40 °C, or even 41 °C. It is accompanied by violent, frontal headaches, myalgia (muscular pain), arthralgia (pains in the joints) and digestive signs such as nausea, vomiting and diarrhoea. Uncontrollable shivering often complete this picture. Two possible courses may be observed at this stage, in the absence of treatment : either complications set in (cf. next chapter), or fever declines, and symptoms resume some time later, producing the famous tertian fever, with bell-shaped fever curves every 48 hours. During these "attacks", the fever drops so suddenly that the patient experiences a loss of temperature balance, and this is restored through profuse sweating. Following a period of remission, the signs may then resume or subside gradually, the latter only in patients whose state of acquired immunity enables them to combat the parasitaemia effectively.

Clinical investigation often shows an enlarged liver, an enlarged spleen and a mucocutaneous icterus clearly indicative of haemolysis. Diminished diuresis (oliguria) may also be observed.

Pernicious attacks or cerebral malaria

This is what the French call "neuropaludisme". It may either follow an uncomplicated attack, or occur from the onset. Apparently the individual is invaded and overwhelmed by

considerable parasitaemia. The schizonts require an oxygen-poor environment in which to develop ; this explains why they migrate to the capillaries of the deep internal organs : essentially the brain, liver and spleen. Electronic microscopy has greatly contributed to knowledge of this process : the red cells parasited by Plasmodium falciparum, located in the deep capillaries, could be seen to undergo surface distortions, throwing out pseudopods, or knobs, which are something like "buttons" that cause the red cells to adhere to the capillaries. This results in a substantial blocking of the blood flow, with a subsequent decreased irrigation of the vital organs such as the brain. The resulting clinical signs correspond to visceral suffering which may be irreversible in the absence of treatment.

Preliminary signs or prodromes may be seen. It is extremely important that they be detected. Most are neurological and psychiatric signs : a slightly clouded state of mind, logorrhoea (the patient talks endlessly), exuberance, surprising behaviour, or apathy and melancholy. This is followed by the onset of the pernicious attack.

Fever is extremely high (41C-42C), the pulse is very rapid (120 beats a minute). A coma develops, and may tend to deepen, with abolition of the deep reflexes.

In children, convulsions are frequently observed. Renal insufficiency, with oliguria, anuria, increased serum creatinine and urea, often completes the picture and may require haemodialysis. Haemolysis produces intense icterus, and clinical investigation reveals the existence of hepato-splenomegaly.

If treatment is not forthcoming, the outcome is inescapably fatal. Occasionally treatment is unable to prevent death. Treatment generally results in recovery with no adverse effects in adults, but children often suffer from psychomotor sequels. This further demonstrates the importance of early diagnosis.

Childhood malaria raises specific diagnostic problems : the clinical picture is less suggestive than in adults, and the course of the disease is erratic. It may be confused with other infections or concomitant diseases whose occurrence is in fact facilitated by malaria itself.

One particular condition requires special mention : visceral malaria. It is the consequence of repeated reinfestations producing naturally acquired immunity which does not suffice to totally check the disease. The body fights the parasites to the point of exhaustion, producing :

– intense anaemia (owing to chronic haemolysis) with pallor, asthenia, oedemas and hypotension. In children it may cause retarded growth and learning difficulties ;
– enlarged volume of the spleen in all cases, due to hyperfunctioning in order to rid the organism of the excessive number of parasites. It may reach a considerable volume (index IV or even V, according to Hackett's classification).

This form of malaria responds well to treatment, but the exhausted body may succumb if the latter is not forthcoming.

Haemoglobinuric bilious fever, or black-water fever

Fortunately this complication is now extremely rare, owing, to a large extent, to the discontinuation of the preventive administration of quinine. The mechanism is not quite

clear, but this accident formerly occurred essentially in persons who took quinine tablets from time to time, in the belief that they would acquire protection against malaria. Although clinically quite similar to a pernicious attack, haemoglobinuric bilious fever is distinguishable by the intensity of haemolysis, the extent of collapse (sudden decrease in cerebral activity or heart collapse) and the appearance of dark red to black urine, an evident sign in an individual with an otherwise very low serum concentration of haematozoans. Medical resuscitation facilities are required for successful treatment, from which quinine must be excluded.

OTHER PLASMODIAL SPECIES (Plasmodium vivax, Plasmodium ovale, Plasmodium malariae) differ from Plasmodium falciparum in their clinical manifestations.

They are never fatal, since parasitaemia is usually low. Since endoerythrocytic schizogony always occurs in the great vessels, the attacks are never too serious.

The existence of latent hepatic forms (hypnozoites or dormozoites) accounts for the possibility of schizogonic recrudescence. Such recrudescence may occur between 1 and 3 years after the mosquito bite for Plasmodium vivax and Plasmodium ovale, and from 15 to 20 years or more after the bite for Plasmodium malariae.

The initial attack or primary invasion precedes the typical schizogonic recrudescence attacks. It is often mild or even asymptomatic, or it may resemble an uncomplicated attack of Plasmodium falciparum, without its extremely serious potential effects.

Two forms of recrudescence attacks are described, corresponding to different plasmodial species.

Benign tertian attacks (P. vivax, P. ovale) and malignant tertian attacks (P. falciparum)

Fever paroxysms occur every third day and are therefore separated by one day of apyrexia (absence of fever). Each attack lasts about ten hours, follows a well-defined pattern and may or may not be preceded by precursor (prodromal) signs such as headaches, nausea or labionasal herpes.

During the shivering stage, or chills, the patient feels cold, has chattering teeth, and covers him or herself as warmly as possible. Fever rises to about 39C and the spleen becomes enlarged. Blood pressure is low. This state lasts for about one hour, and is followed by the hot stage ; this time the patient is too hot and rejects all covers. The skin is dry and burning, fever rises to 40 or even 41. Headaches are severe. Exposure to light is intolerable (photophobia), and the conjunctiva are red. The volume of the spleen has decreased, however, whereas the pulse remains rapid and blood pressure rises. Passing of urine is diminished. At the end of 3 to 4 hours, the sweating stage begins ; its duration is similar. Sudation is profuse, drenching the clothing, bedclothes or bed mat. The body temperature falls, sometimes below normal (hypothermia). Urination resumes, with large amounts of urine. The patient experiences euphoria, feels "resuscitated", to the point of desiring to leave the bed, but in fact very rapidly feels weak and exhausted.

Quartan fever (P. malariae)

The clinical picture is the same, but paroxysms occur every fourth day, separated, then, by two days of apyrexia.

A special case : mixed parasite infestation

When mixed parasite infestation is encountered, and one of the plasmodial species involved is Plasmodium falciparum, the clinical manifestations and risk of complications observed in the latter prevail.

Last, the clinical manifestations of drug-resistant malaria are quite specific, and are increasingly well known. They will be discussed in the chapter on drug resistance.

DIFFERENTIAL DIAGNOSIS

Clinically speaking, any fever occurring within an endemic area or in a person who has recently left an endemic area should be viewed as a possible case of malaria (except when prophylaxis is judged to be effective - no resistance to the drug administered - and correctly applied).

The question of a differential diagnosis in all fever cases then arises.

Symptoms may be suggestive of meningitis, the first septenary of salmonellosis, arbovirosis, influenza, an intestinal toxinfection, a pre-icteric phase of viral hepatitis, etc.

The diagnosis is much more delicate in the case of chloroquine-resistant malaria occurring in patients under prophylactic treatment : symptoms are often quite misleading, and abnormal clinical and biological signs may be evocative of a number of conditions quite different from the actual cause.

Clinical signs may be attenuated, leading the practitioner to consider a diagnosis of visceral malaria : asthenia, anaemic syndrome, hepato-splenomegalia, intermittent fever, all of which follow a slow course. In such cases attacks are frequently observed long after the discontinuation of prophylaxis.

Pseudo-influenzal forms, suddenly developing into a pernicious attack, have been described. Neurological signs then occur without warning, with no fever or symptoms immediately suggestive of malaria.

Clinical manifestations often depend on the patient's immune status and on the existence of prophylaxis. Non-immune persons (travellers, expatriates, infants) are the main victims of these resistant forms of malaria.

In these resistant conditions, parasitaemia may be very slight, to the point of being impossible to detect in patients undergoing partially ineffective prophylaxis. When clinical signs indicative of a severe condition do develop, a very high level of parasitaemia is generally present, requiring an exchange transfusion in some cases.

BIOLOGICAL DIAGNOSIS

Direct tests

Since the Plasmodium is a haematozoan that parasites the red blood cells, testing concentrates on the blood, in which the different blood schizogony forms of the parasite are detected. Only two tests provide proof of malarial infection : the smear test and the thick drop.

These tests are easy to perform. The blood is drawn from the finger tip (this avoids taking large amounts of blood, especially in anaemic or undernourished children). Following careful disinfection, an incision is made using a stylet and the drop of blood obtained is placed on two spots on the plate. In one place it is haemolysed for the thick drop, in the other it is spread to a thin film. The May-Grünwald and Giemsa stains are used, either in conventional preparations or in ready-to-use test kits.

Reading is done very rapidly. The thick drop is valuable in that it detects low parasitaemia, while the thin film clearly shows which plasmodial species is involved, a most important piece of information indicating the risk of subsequent evolution.

Quantification of parasitaemia is also important, be it only for the proper surveillance of its decline and disappearance following treatment. The results are expressed as a percentage of parasited red cells, the number of parasites per mm3 of blood or the number of parasites for 1,000 white blood cells. The intensity of parasitaemia may vary ; it is usually high in severe attacks, but exceptions are known to occur.

In the specific case of a Plasmodium falciparum attack with complications, the parasite-packed red cells are all concentrated in the deep capillaries. For this reason, blood tests may be negative and must be repeated.

When attacks are observed in patients under prophylaxis who have been infested with strains resistant to the drug being used, parasitaemia is often extremely low and its detection may occasionally require repeated tests.

Complementary investigatory techniques are increasingly used, and provide a valuable contribution. These include :

Indirect indicators

Abnormal haemograms are observed.

Regenerative haemolytic anaemia is the rule. It may be extremely widespread in case of concomittant haemolysis in severe attacks. It is also seen in visceral malaria in which the chronic, subclinical attacks tend to diminish the number of red cells. This is one sign of asymptomatic conditions with drug-resistant strains continuing to develop despite prophylaxis.

Leukopenia may be observed, but hyperleukocytosis is often seen in pernicious or initial attacks.

Thrombocytopenia (or decreased platelet count) is very frequent, and may be accompanied by purpura.

Liver ailments are frequent : increases in transaminases and in alkaline phosphatases, increased bilirubin level. When a lipid assay can be made, it is found to be disturbed, with definite hypocholesterolaemia and, frequently, hypertriglyceridaemia.

Other disorders are observed in complicated cases : kidney failure is accompanied by an increase in urea and creatinine levels. The presence of soluble immune complexes often produces diffuse intravascular coagulation.

Testing for serum antibodies, generally using indirect immunofluorescence, is also of diagnostic value. It is mostly performed during epidemiological surveys. In the diagnosis of acute cases, testing for plasmodia using thin film and thick drop techniques is most reliable since it is rapid, inexpensive and capable of distinguishing the parasite species incriminated.

ANTIMALARIAL DRUGS

The ideal drug for treating malaria should :

- be active at all stages of the life cycle of all plasmodial strains ;
- act selectively on the parasite ;
- be easy to employ in all individuals, and produce no side effects.

None of the available drugs corresponds to this ideal. For this reason, treatment of malaria requires a perfect understanding of the mode of action as well as of the advantages and disadvantages of each drug.

Since ancient times Cinchona bark has been known to treat "intermittent fevers" (malaria). The exact date at which this remedy was introduced to Europe is not known, but the fact that Spanish priests brought it to Rome in 1632 seems to be accredited. Cinchona powders were used before people had any accurate notion of the amount needed for effective use, whence the alternation of successful treatment and failure. In 1820, cinchona alkaloids were isolated. No further progress was made in antimalarial therapy until 1940. At that date, the synthesis of chloroquine ushered in the era of antimalarial drugs.

In 1944, other 4-aminoquinolines were synthesized, producing amodiaquine. Proguanil and pyrimethamine saw the light in 1950. Over 250,000 compounds were screened in the 1960's, by a number of research institutes. These investigations produced several other classes of antimalarial drugs such as the quinolinemethanols or the phenanthrenemethanols.

Two main groups of antimalarial drugs may be distinguished on the basis of their point of impact :

- schizonticides ;
- gametocytocides.

The schizonticides, which include most antimalarial drugs, act on the endoerythrocytic forms. They combat the clinical symptoms and have a prophylactic effect when administered in sufficient amounts.

The gametocytocides act on the potentially sexual forms, the gametocytes, which are capable of ensuring transmission of the disease to anophelines, thus maintaining malarial endemicity. They also combat hepatic tissue forms, thus protecting the individual against recrudescence induced by some species such as Plasmodium vivax, Plasmodium ovale and Plasmodium malariae. Unfortunately they are poorly tolerated, dangerous and difficult to manage.

The only natural antimalarial drug is quinine, all others are synthetic.

SCHIZONTICIDES

Quinine

Quinine is an alkaloid yielded by cinchona bark. An alkaloid is an organic, basal substance, necessarily of plant origin, with at least one atom of nitrogen in its molecule (digitalin and morphine are alkaloids).

It is extremely fast-acting : it is absorbed very quickly when taken orally, and may be administered parenterally (intravenous infusions, intramuscular injections). It is eliminated rapidly as well : it is totally evacuated from the kidneys within 24 hours. For this reason, intake must be repeated around the clock to make sure an effective serum concentration is maintained at all times.

It is believed to act by inserting itself in the parasite's DNA (Desoxyribonucleic acid) at several levels ; this would explain why resistance is less frequent than with other drugs.

Quinine remains the best emergency drug (in pernicious Plasmodium falciparum attacks), since it combines rapid effectiveness and possible intramuscular or intravenous use when the oral route is excluded (in uncontrollable vomiting or coma, for instance).

It is generally available in the form of quinine salts : QUINIMAX® (quinine, resorcine, quinidine, cinconidine), QUINOFORME® (basal quinine formiate), QUININE LAFRAN® (quinine hydrochloride), etc.

Being a basal substance, quinine is caustic :

— when used intramuscularly, it may produce indurations at the injection site, abscesses, necrosis of the skin. Deep intramuscular injection in the upper external quadrant of the buttock, respecting perfect asepsis, is therefore a must in order to avoid inoculation tetanus and permanent damage to the sciatica (causing paralysis of the lower limb).

— when used intravenously, endophlebitis and sclerosis of the infused vein may be observed. If performed too rapidly, an injection may induce quinine shock, which takes the form of headaches, impaired vision and hearing (tinnitus aurium : hearing bells ringing), disturbed equilibrium, low blood pressure and electroencephalographic disturbances. These manifestations are part of what is commonly called cinchonism.

Severe hypoglycaemia due to the stimulation of insulin secretion has also been described.

Two questions are often raised :

— does quinine induce abortions ? Not at the usual doses, but it may stimulate the uterus during delivery when labour has already begun ;

— does quinine play a role in the development of "black-water fever" ? Bilious haemoglobinuric fever was well known during the "colonial" era. It occurred when quinine prophylaxis was indefinitely pursued, and was in fact the result of hypersensitization of an immunological type, with kidney involvement (highly evocative red-black urine) and collapse, often fatal.

The 4-aminoquinolines

The leading members of this family are chloroquine (NIVAQUINE®) and amodiaquine (FLAVOQUINE®, CAMOQUIN®). These drugs are rapidly absorbed, although less so than quinine, and are evacuated more gradually : fractionation of doses is not necessary.

4-aminoquinolines tend to aggregate within the nucleus of the parasite enclosed in the red blood cell. They prevent the replication of the parasite's DNA by inserting themselves in the double helix, and prevent growth in the plasmodium. They may also act by interfering with utilisation by the parasite of the haemoglobin within the red cell.

The preferred administration route is the oral route, although intramuscular use of cloraquine (NIVAQUINE®) is possible, but the intramuscular injection of this product is formally contraindicated in children under 5, since it may result in fatal collapse.

4-aminoquinolines are used to treat acute episodes of malaria when oral administration is possible (they are used in chronic conditions). For many years they were given for prophylactic purposes. The limits of this treatment are of course set by the extensive spread of plasmodial resistance to these drugs.

The disadvantages of their use in tropical areas have often been described. In addition to tasting bitter, they may cause headaches, vertigo, blurred vision, nausea and anorexia, as well as a slate-gray pigmentation of the mucosa and of the matrix of the nails, which is seen in case of prolonged prophylactic administration.

More specifically, in the case of chloroquine (NIVAQUINE®), patients have complained of intense, exacerbated itching in recent years : this has been explained in some individuals by the microfilaricidal action of chloroquine. When large amounts are given, as is often the case in the treatment of systemic diseases such as lupus and rheumatic fever, ocular disorders such as corneal deposits and chorioretinitis have been reported, along with rotatory vertigo and mental disorders.

Overdose reactions are mostly observed in Africa during suicide attempts, when more than 2 grams are taken. The main manifestations are disturbed heartbeat and cardiorespiratory shock resulting in death. Diazepam (VALIUM®) is currently successfully used in 90 % of suicide attempts with chloroquine, provided they are caught in time, of course.

Two types of extremely serious adverse reactions have been reported with amodiaquine : one is agranulocytosis, the other is toxic hepatitis, which may be fatal. In some countries, amodiaquine has been taken off the market, while its prophylactic use is no longer recommended in others.

Antifolates

These include some sulfonamides and the sulfones. They act more slowly than quinine and the 4-aminoquinolines ; some are even long-acting.

The main sulfonamide is sulfadoxine (FANASIL®), while the major sulfone is dapsone (DISULONE®).

Their antimalarial action is explained by the inhibition of the transformation of para-aminobenzoic acid, a necessary step in the maturation of the intra-erythrocytic plasmodium. This is attained through the inhibition of the dihydrofolic acid synthetase enzyme.

They are used to treat acute attacks, and are advantageous in that only a single dose is required ; this contributes substantially to patient compliance. They are often used in

association with other antimalarial drugs. Oral and injectable forms are available. Their use is limited by their contraindications and the adverse reactions produced.

Their administration is strongly disadvised in areas where meningococcic cerebrospinal meningitis is endemic (the meningitis belt), where it may contribute to the development of sulfonamide resistance in meningococcal strains.

Adverse reactions are serious (macrocytic anaemia due to folic acid deficiency) to fatal (erythema multiforme, Stevens-Johnson syndrome, peri-orificial erythema, Lyell's syndrome, acute epidermic necrosis).

It is not prescribed during pregnancy.

Resistance to the sulfonamides has developed very rapidly.

Antifols

These are biguanides, the best known of which are proguanil (PALUDRINE®), pyrimethamine (MALOCIDE®) and trimethoprime (a component of BACTRIM®).

They inhibit the transformation of the para-aminobenzoic acid required by the plasmodium, by blocking the dihydrofolate reductase activity. This inhibition only affects the plasmodial enzyme, to the exclusion of mammal cells ; this explains its non-toxic antimalarial action.

The excessively slow action of proguanil makes it a mediocre curative drug, but it is occasionally preferred for prophylaxis (particularly in English-speaking countries, where it is available).

Its toxicity is slight and it is very well tolerated. Unfortunately many strains of Plasmodium vivax and Plasmodium falciparum have developed resistance to this drug.

Pyrimethamine (MALOCIDE®) is very slow-acting. It crosses the placental barrier and is formally contraindicated in pregnant women owing to the risk of foetal malformations. It may cause macrocytic anaemia through folic acid deficiency.

Many strains of Plasmodium vivax and Plasmodium falciparum are now resistant to this drug.

Mefloquine

This is an aminoalcohol of the quinolinemethanol type (LARIAM®). It is administered orally and is useful in the treatment of acute attacks and for prophylaxis. Effective blood concentrations are reached within 4 hours, and this compound persists within the body for long periods (up to about 30 days). This explains why it may be used in acute treatment, on the one hand, and also why very low doses may be used in prophylaxis to maintain effective serum concentrations.

The treatment schedule is simple : it is given on a single day, which makes patient compliance easy. The advantage of this compound is that it is active against practically all plasmodial strains, including those that are resistant to the usual antimalarial drugs. Only a few cases of drug resistance have been reported in South-East Asia. In vitro tests have shown diminished sensitivity in some West African strains, although the drug is not commercialized in that area. No correlation has been shown with in vivo tests.

The disadvantages of mefloquine (LARIAM®) are connected with its side effects, which are mild in prophylaxis but much more marked in acute treatment. They include a feeling of inebriety, vertigo, nausea, impaired equilibrium, diarrhoea, abdominal pain, drowsiness and headaches. It should not be given to children weighing less than 15 kilos or to pregnant women.

Halofantrine (HALFAN®)

HALFAN® is the most recent of the antimalarial drugs of the phenanthrenemethanol category. It is administered orally in either tablet or drinkable fluid form, to both adults and children of all ages, but is only given in acute attacks. This drug is not used for prophylaxis. It is currently available in most western African countries.

It is easy to use, since the treatment period lasts only 1.. hours (3 doses at 6-hour intervals). Absorption occurs rapidly, with effective concentrations reached within about 4 hours. Its half-life is 3 to 5 days, which is much longer than that of mefloquine. Its therapeutic efficacy is excellent : halofantrine combats all existing plasmodial strains. No resistance has been reported to date, and in vitro testing shows it to be active at infinitesimal concentrations.

Tolerance is excellent, and only some cases of abdominal pain have been recorded.

It is contraindicated during pregnancy.

Drug combinations

Often a combination of two compounds acts more effectively than each of the drugs taken separately, owing to potentialization or synergetic action, and the required dose of each component drug may be reduced.

SULFONAMIDES + PYRIMETHAMINE = FANSIDAR®

The dosage forms are oral and injectable, and it has been prescribed in a single dose, for curative purposes, up to now. Its action is not very rapid, and it is therefore not suitable for use in severe cases.

Many plasmodial strains have rapidly developed resistance to FANSIDAR®.

Its side effects and contraindications are the same as for each of its two components.

SULFONES + PYRIMETHAMINE = MALOPRIM®.

Mostly used for prophylaxis. It has the same side effects and contraindications as each of its two components.

MEFLOQUINE + SULFADOXINE + PYRIMETHAMINE = FANSIMEF®

The dose of mefloquine recommended when used alone may be halved for treatment with this drug combination. This combination is suggested in the curative treatment of malaria attacks in areas where multiresistance prevails.

It has the same disadvantages as each of its components.

Antibiotics

The cyclines are known to be minor antimalarial drugs, but valuable results have been attained by combining them with other drugs, and especially quinine, in areas where strains show multi-drug resistance (South-East Asia).

Doxicycline is the most frequently used compound in this category, but its use is limited by its contraindication in pregnant women and children under 8 years of age. Use of these drugs is still relatively infrequent.

GAMETOCYTOCIDES

The only ones known are the 8-aminoquinolines (Primaquine).

They affect the gametes, thus interrupting the chain of transmission of malaria from an infected human host to the vector mosquito. They are also active in the tissue stages of plasmodium vivax and ovale. They are unfortunately highly toxic and are rarely employed. Cases of methaemoglobinemia and agranulocytosis have been described, as well as acute haemolytic complications, particularly in individuals with G-6-PD deficiency, a frequent occurrence in Africans. These drugs have been withdrawn from the French market but are still found in English-speaking countries.

DRUG RESISTANCE

It affects strains of Plasmodium falciparum. In severe and even fatal clinical manifestations of malaria, this plasmodial strain is always involved. Plasmodium falciparum has always killed people, and continues to kill them, but the problem is compounded by the fact that it kills them differently at present. Indeed, a new obstacle has arisen, and it reduces the effectiveness of therapeutic efforts : it is drug resistance.

In the case of malaria, WHO defines resistance as "the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to, or higher than, those usually recommended, but within the limits of tolerance of the subject".

Resistance develops when the microorganisms proliferate very rapidly and undergo spontaneous mutations resulting in their transformation into slightly different strains within a short lapse of time.

Resistant mutants possess a modified genome that enables them to survive either by using alternative metabolic routes to those blocked by the drug, or by preventing the drug from entering the cell.

Although each of the four malarial parasites may develop drug resistance, P. falciparum is the main concern, since it develops resistance to blood schizonticides and to chloroquine in particular. No other malarial parasite has developed resistance to this drug.

CHANGING GEOGRAPHICAL DISTRIBUTION OF RESISTANCE

Chloroquine (NIVAQUINE®) was the first drug to be affected by this phenomenon : resistance began in the 1960's, where it occurred both in the forested equatorial areas of South America and in South-East Asia.

It has gained ground regularly throughout Asia (in the Indochinese peninsula, the Philippines, Indonesia, southern China and Pakistan). In South America it affects every forested area with an equatorial climate (in Brazil, French Guiana, the forested regions of Ecuador and Venezuela, and Colombia).

In Africa, resistance developed and spread at a later date. The possibility of its existence in eastern Africa was first mentioned toward 1975. It was limited to Kenya and Tanzania, at the time, but then spread to Sudan and Zambia, and severely affected Madagascar. Only in 1984 did it reach Namibia, Angola and Malawi. Ten years after the initial reports it arrived in central Africa (the Central African Republic, Zaire). In 1985-86, limited foci of resistance were observed in the Congo, Gabon and Cameroon. Since 1986, several concomitant phenomena have been observed :

— an increase in the number of chloroquine-resistant plasmodial strains. Resistance is defined in terms of intensity : in Kenya it is 70 %, in Gabon it rose from 3 % to 23 % in 2 years, while it is somewhere around 90 % in South-East Asia ;

— an extension of its geographical area, to West Africa. Several strains have proved resistant in the following countries : Benin, Togo, Ivory Coast, Burkina-Faso, Senegal. The problem is still of a limited nature in these countries, but there is no foreseeing what the future holds in store ;

— extension to other drugs : there is now a cross-resistance with the other 4 aminoquinolines of the FLAVOQUINE® type. It seems to be correlated with the degree of chloroquine resistance : these drugs are still relatively effective in areas where chloroquine resistance is low, but ineffective in those areas with intense chloroquine resistance.

The combination of a sulfonamide (sulfadoxine) with pyrimethamine (FANSIDAR®) was long believed to be an adequate response to chloroquine resistance. Resistance to this product was soon reported, however : while it occurs essentially in South-East Asia, where 60 to 70 % of strains are affected, it is also present in East Africa (40 % of strains) and to a lesser extent in West Africa. It is important to note that this resistance spreads rapidly and very quickly reaches a high level of intensity.

The problem is different for quinine salts (QUINIMAX®, QUINOFORME®), since true resistance has only developed slowly, and its geographical location is quite limited. It is seen on the Thailand-Burma-Cambodia border, in forested parts of South America (Guyana, Brazil) and in East Africa (Mozambique, Kenya, Burundi).

In other areas, diminished sensitivity to quinine has been reported.

Resistance to pyrimethamine only (DARAPRIM®, MALOCIDE®) as well as to proguanil (PALUDRINE®) occurred at an early date : in the latter case Plasmodium vivax strains are also involved.

Fortunately, advances in antimalarial chemotherapy have produced new molecules. Resistance to mefloquine (LARIAM®) has been encountered in South-East Asia. Some plasmodial strains seem to show in vitro resistance to this substance in West Africa (Nigeria, Benin).

The last-born of the antimalarial drugs, Halofantrine, sold under the trade name of HALFAN®, inhibits the growth of multiresistant Plasmodium Falciparum strains when administered in concentrations close to the nanomole. No resistance to it has been recorded so far, although it has been widely used for therapeutic trials.

TESTING FOR RESISTANCE

Two types of tests may be performed to determine the type of drug resistance. One type is in vivo, the other in vitro.

In vivo tests, based on response to treatment, are used to determine the degree of sensitivity or of resistance of each specific strain to a given drug by monitoring the evolution of parasitaemia :

— susceptibility "S" : disappearance of the asexual parasite forms within 7 days (no recrudescence) ;

— resistance :

● "RI" : the same as "S", but early or late recrudescence ;

- **"RII"** : parasitaemia is reduced but not eliminated ;
- **"RIII"** : no marked reduction in parasitaemia (the initial figure is reduced by less than 25 %).

It is very important to distinguish between true recrudescence and possible reinfestation (that is, reinoculation of parasites following a mosquito bite), but in endemic areas where anophelines abound, this is particularly difficult.

The response "in vivo" - that is, in a person affected with malaria - is therefore correlated with an "in vitro" test of the plasmodial strains responsible for the disease. It is important to note that plasmodial strains found to be resistant in vitro may still respond in vivo. No hasty conclusions should be drawn, then, from in vitro test results.

The in vitro tests assess the ability of increasing doses of an antimalarial drug to prevent schizont formation. The method consists of placing erythrocytes parasited by a given plasmodial strain (obtained by taking a specimen of a patient's blood) in contact with an antimalarial drug. The results are expressed in terms of the Minimal Inhibiting Concentration (MIC), or the Inhibiting Concentration for 50 % of multiplication (IC 50).

All antimalarial drugs may be tested in this way, and an "antimalariogram" may be established for a given strain. Testing may assess sensitivity to chloroquine, monodesethylamodiaquine (an active metabolite of amodiaquine), quinine, FANSIDAR® and mefloquine, and systematic assessment of halofantrine will soon be forthcoming.

This method is a most valuable epidemiological tool, since it may be used to monitor the development of resistance, and when implemented rapidly it enables the proper adjustment of treatment. A global approach to the problem of drug resistance is made possible by the correlation of in vitro and in vivo findings.

To claim that the pathogenesis of plasmodial resistance to antimalarial drugs has been elucidated would be presumptuous. New theories are constantly being constructed as complementary findings are assimilated by the existing models. Until now, drug pressure was believed to be the main factor.

Drug pressure means that a drug utilization within a specific population group is sufficient to affect the target at which it is aimed. The selection of drug-resistant haematozoan strains has been strongly influenced by self-prescribed treatment courses for ailments that are not necessarily patent cases of malaria, and by the haphazard administration of chemoprophylaxis. Drug dosage is often sub-curative.

Other characteristics to be taken into consideration are the type of transmission (seasonal or permanent) and the level of population immunity. Chemoprophylaxis administered irregularly to a population with a low level of immunity favours the transmission of selected strains, and therefore the extension of drug resistance.

Geographical distribution of chloroquine resistance

Countries in group 1

No Plasmodium Falciparum or no recorded chloroquine resistance.

America : Argentina, Belize, Chile, Costa Rica, Dominican Republic, Guatemala, Haiti, Honduras, Mexico, Nicaragua, northern Panama, Paraguay, El Salvador.

Asia : China (North-East), Maldives, Nepal.

Middle East : Afghanistan, Iran, Irak, Oman, Saudi Arabia, United Arab Emirates, Syria, Turkey, Yemen, Southern Yemen.

Africa : Djibouti, Chad, Egypt, The Gambia, Guinea Bissau, Guinea, Liberia, Mali, Mauritania, Niger, Senegal, Sierra Leone, Somaliland, Cape Verde, Mauritius, Sao Tome and Principe Islands.

Countries in group 2

Presence of chloroquine resistance.

America : Bolivia, Panama (southern), Peru.

Asia : Bangladesh, Bhutan, Brunei, India, Indonesia, Malaysia, Pakistan, Sri Lanka.

Oceania : Papua-New Guinea, Solomon Islands, Vanuatu.

Africa : Angola, Burkina Faso, Botswana, northern Cameroon, Central African Republic, Comoros, Ethiopia, Ghana, Ivory Coast, Madagascar, Namibia, Nigeria, South Africa (Transvaal, Natal), Sudan, Swaziland, Togo, Uganda, Zambia, Zimbabwe.

Countries in group 3

High prevalence of chloroquine resistance and multiresistance.

America : Brazil, Colombia, Ecuador, French Guiana, Guyana, Surinam, Venezuela.

Africa : Benin (Cotonou area), Burundi, southern Cameroon, Congo, Equatorial Guinea, Gabon, Kenya, Malawi, Mozambique, Rwanda, Tanzania, Zaire, Zanzibar.

Asia : Burma, Cambodia, China (southern states and Haï-nam), Laos, Philippines, Thailand, Viet Nam.

Important note : Transmission of malaria is nonexistent (in America and Asia) or infrequent (in Africa) in urban settings.

PROPHYLAXIS

It is two-sided, involving :

— measures aimed at controlling or affording protection against the vector of malaria, the mosquito ;

— measures aimed at controlling or preventing the action of the malarial parasite - the Plasmodium - within the body.

GLOBAL ANOPHELINE CONTROL

Hopes of the eradication of malaria were based on this strategy. The main commonly used insecticides include :

The organochlorines

DDT (dichloro-diphenyl-trichloro-ethane) is active when in contact with most insects : it is a nerve poison for arthropods. It is mildly toxic and persists for long periods of time when sprayed on walls. It is said to be residual. For many years DDT was the main means of vector control in malaria. Campaigns for the spraying of the indoor walls of homes were widely implemented. These were effective over a period of time, after which the first instances of insect resistance to this compound were observed, and have spread constantly thereafter. This type of action has gradually been given up.

HCH (hexachlorocyclohexane) and dieldrine are toxic, much less residual and have also produced many instances of resistance.

Organophosphorus compounds

They act by inhibiting an enzyme - acetylcholinesterase - without which the nerve impulse cannot be properly transmitted ; the ensuing neurological anomalies cause the death of the insect.

These insecticides have a low toxicity for man if they are handled with care, and have also been used in spraying campaigns for vector control. Malathion and fenitrothion are exemplary of these. Unfortunately, resistance to them has also developed.

To summarize, the development of resistance has put an end to many vector control projects, and this direction is presently completely blocked by the prohibitive cost of efforts to develop and utilize new insecticides.

Insecticides were used in conjunction with broad action aimed at limiting the larval habitats of mosquitoes : drying up of marshlands, clearing of muddy roads whose ruts are ideal breeding places, collecting of hollow rubbish such as tins, tyres, jars, etc, in which water stagnates.

At present, action directed against the malarial vector is limited to individual efforts to achieve protection against infecting mosquito bites :

— use of slow-burning pyrethrum coils ("Chinese mosquito coils") ;
— use of mosquito repellent sprays and lotions applied to the skin : diethylotolnamide (ZZ TOPR), citronella, etc. More recently, there is a renewed tendency to view mosquito nets as an effective means of vector control. Many trials of mosquito nets saturated with insecticides of the deltamethrine type (a member of the pyrethroid group) have been conducted. Contact with these mosquito nets was found either to exterminate mosquitoes or to reduce their infectivity enormously, a most advantageous feature for other, unprotected persons in the area. These mosquito nets will increasingly be available at a reasonable price.

CHEMOPROPHYLAXIS

It is now highly controversial, owing partly to the development of drug resistance and secondly, to the fact that it is considered partly responsible for the occurrence of resistance. Two different types of chemoprophylactic approaches may be defined, according to the situation encountered :

— one approach for inhabitants of endemic areas : for people who spend more than 6 months there, either for a prolonged work mission, or because they are "natives" ;
— another approach for travellers spending a short period of time in the endemic area (less than 2 months).

For the first category, people living in endemic areas, chloroquine (NIVAQUINE®) is the only acceptable drug for use in areas where chloroquine resistance is totally absent or slight. A figure of up to 20 % of resistant strains may be considered acceptable for an area, provided people given prophylaxis are monitored for the detection of any manifestation of fever. This indicates how important it is to determine as accurately as possible the intensity of chloroquine resistance in each country and within a given country, since maps of intensity of chloroquine resistance show the existence of complex patterns.

When the intensity of resistance is acceptable, special attention should be given to the protection of two population groups :

— pregnant women, who are more susceptible to malaria ;
— infants, since they run a vital risk during pernicious attacks.

Only CHLOROQUINE may be used, at the dose of 600 mg a week (six 100 mg tablets or two 300 mg tablets) in adults, and 25 mg every two days in children under 1 year old, and 25 mg to 75 mg daily between ages 1 and 12 years.

None of the other antimalarials can be used, either because their administration over prolonged periods of time is not advisable, or because they are no longer indicated for prophylaxis, owing to the occurrence of serious side effects.

There are several schools of thought on long-term chemoprophylaxis : some people feel that it should not be employed, so as leave individuals with the possibility of developing natural immunity.

The second category of people includes travellers who do not live in endemic areas, or those who originate from such areas but have lived in non-endemic areas for more than 2

years (migrant workers and their children). They must be given prophylaxis during a short stay (less than two months). This population group is particularly exposed to malaria, since immunity is nonexistent, or has been lost (in the case of migrant workers).

When the level of chloroquine sensitivity is still high, and when at-risk groups are involved (pregnant women and infants), chloroquine (NIVAQUINE®) is given :

- starting on the first day of the stay ;
- throughout the stay ;
- during 6 weeks after the end of the stay.

Adults are given 600 mg a week, in six 100 mg doses or two 300 mg doses.

Children under one year old are given 25 mg every two days.

Children aged 1 to 12 years are given 25 to 75 mg daily (doses are adjusted for age).

When chloroquine resistance is intense, mefloquine (LARIAM®) may be prescribed, provided the limits of its utilization are kept in mind :

- in adults, 250 mg a week, or 1 tablet ;
- in children weighing 15 to 20 kg, 50 mg a week, or 1 tablet ;
- in children weighing 20 to 30 kg, 100 mg a week, or 2 tablets ;
- in children weighing 30 to 45 kg, 200 mg a week, or 4 tablets.

Medication is begun one week before departure, is pursued throughout the stay and continued 6 weeks after the end of the stay.

In addition to these measures, quite a specific role has been left to presumptive treatment. This is a self-administered treatment with no biological proof of disease, taken in the presence of clinical signs suggestive of malarial pathology : the main symptom here is fever. It is called for in a very definite category of cases, where chemoprophylaxis is clearly impossible, either because drug resistance is too intense or because of an excessively long stay in an endemic area, or last, because the administration of other drugs makes the use of NIVAQUINE® impossible.

The drug employed in this case is administered according to the therapeutic schedule. The following should be preferred :

- mefloquine (LARIAM®), within the limits imposed by its side effects ;
- halofantrine (HALFAN®), the drug of choice, given its excellent tolerance ;
- quinine salts, in the form of orally administered tablets when the above-mentioned drugs are not available.

The limits of this type of presumptive treatment reside in the fact that many of the fever manifestations that prevail in the tropics have a close resemblance with malarial paroxysms, and drug intake cannot be taken "ad libidum" whenever a fever occurs.

This therapeutic attitude should therefore only be authorized exceptionally, and as a last resort in extreme situations when a definite diagnosis is out of the question.

TREATMENT

PRESCRIPTION SCHEDULES

Prescribers should keep in mind the fact that any fever case suggestive of an episode of malaria is a potential emergency, since there is always the risk of a pernicious attack.

One **absolutely fundamental** rule where malaria is involved is that one must act without waiting, for delayed treatment often results in the occurrence of severe forms.

As shown above, there is no longer any standard, universal treatment for episodes of malaria. What, then, should be done ?

First, it is important to gather information on the geographicalal distribution of endemicity, the existence of adequate or inadequate prophylaxis, any previous appropriate treatment, adequately managed either by the prescriber or by the patient. It is also essential to make an assumption as to the patient's immune status with respect to malaria : infants, as well as children and adults originating in malarious areas but having spent several years outside of any such country, travellers from western countries, patients whose defenses have been lowered by multiple infections should all be presumed to have insufficient protection.

A second important phase is the analysis of the clinical picture and symptomatology : is this an uncomplicated attack, an attack complicated by digestive symptoms that compromise the efficacy of oral drug administration (vomiting, profuse diarrhoea), or a pernicious attack, in which consciousness is already impaired ?

Once this information is available, the choice is facilitated.

It should be recalled that treatment must be appropriate, administered at effective doses and for a sufficient length of time. Excentric prescription schedules have been the cause of disasters.

TREATMENT OF UNCOMPLICATED ATTACKS

• *When no chloroquine resistance or multiresistance is suspected*

In adults

Chloroquine (NIVAQUINE®) should be administered orally (100 mg or 300 mg tablets) for a total dose of 40 mg/kg spread over a 5-day period, or, in other terms, a treatment course of five 100 mg tablets taken for 5 days.

It is advisable to prescribe a prophylactic course following treatment.

In children

The total dose is 10 mg/kg of chloroquine (NIVAQUINE®) spread over 5 days. Syrup form should be preferred in infants, and tablets for older children.

• *When chloroquine resistance is suspected*

In adults

Prescription, depending on availability, of :

— FANSIDAR®, a single dose of 3 tablets, in accordance with the instructions ; the contraindications must be respected and side effects kept in mind ;

— HALFAN®, the latest antimalarial, 250 mg tablets. Three 500 mg doses, for a total dose of 1,500 mg, taken at 6-hour intervals (for a total treatment duration of 12 hours). This treatment is effective and extremely well tolerated ;

— LARIAM®, 250 mg. A first dose of 3 tablets (750 mg) is followed by 2 tablets (500 mg) 8 hours later, then 1 tablet (250 mg) another 8 hours later, for a total dose of 1,500 mg. This treatment is highly effective but patients must remain in bed, owing to side effects such as vertigo and a feeling of inebriation.

In children

Recommended prescriptions :

— HALFAN®, in the form of a solution for paediatric use, at a total dose of 24 mg/kg in three 8 mg/kg doses at 6-hour intervals (duration of treatment, 12 hours). This treatment may be prescribed at all ages ;

— LARIAM®, (50 mg tablets). May be prescribed for children weighing more than 15 kg, according to the following schedule : 25 mg/kg in one or two doses (either one 250 mg tablet or five 50 mg tablets for 10 kg of body weight). Tolerance of this compound seems to be superior in paediatric use than in use with adults.

TREATMENT OF ACUTE MALARIAL ATTACKS WITH DIGESTIVE DISORDERS

Parenteral administration of FANSIDAR® is recommended (provided no resistance to this compound is suspected, and with full awareness of the limits of its utilization), or quinine salts (QUINIMAX®, QUINOFORME®, QUININE® formiate, etc).

In adults

One intramuscular injection of FANSIDAR® (2 ampoules) or intramuscular injection of quinine (3 ampoules on the first day, followed by 2 ampoules on the second day, gradual administration over the 24-hour period).

In children

FANSIDAR® should be prescribed in intramuscular injections adjusted to the child's weight, with an average of one-half ampoule per 10 kg of body weight, in a single injection.

Quinine salts should be prescribed by the intramuscular route, making sure that asepsis and the injection of 25 mg/kg and per day, administered in three doses, are strictly respected. The dosage forms of the different types of quinine salts on the market should be taken into account in calculating the doses to be administered.

Following this parenteral treatment, complementary oral treatment is recommended as soon as the digestive symptoms disappear :

— in areas still sensitive to chloroquine, this compound should be used :

— in areas where chloroquine resistance prevails, quinine salts may be given in tablet form, at the dose of 1 g daily in adults, and 0.15 g per year of age in children, with intake spread over a 24-hour period, for 8 to 10 days.

TREATMENT OF PERNICIOUS ATTACKS

Definition of severe or complicated malaria (including pernicious attacks) requiring urgent parenteral treatment (WHO definition).

Presence of Plasmodium falciparum and of one (in group A) or several (group A only or groups A + B) of the following manifestations :

A - Major

1. Cerebral malaria : coma phase II or more (strict definition of a pernicious attack)
2. Repeated generalized convulsive seizures (more than 2 per 24 hours)
3. Renal failure (diuresis < 400 ml/24 h, creatinine > 265 µmol/l)
4. Pulmonary oedema
5. Hypoglycaemia (< 2.2 mmol/l)
6. Collapse
7. Diffuse bleeding
8. Blood acidosis (art. pH < 7.25 or bicarb. < 15 mmol/l)

B - Minor

1. High parasitaemia

Non-immune individuals > 100,000/mm^3 > 2 %
Semi-immune individuals > 500,000/mm^3 > 10 %

2. Icterus (bilirubin > 50 µmol/l)
3. Hyper or hypothermia (> 41 or < 36 °C)
4. Severe normocytic anaemia (Th < 20 %, Hb > 5 g/dl)

Intravenous infusions of quinine (either in a bottle of glucose solution or using a continuous administration pump) is the **ONLY** possible, active treatment.

In adults, the dose is 1.5 g/24 h, administered in three 3-hour infusions (500 mg of quinine salts in 250 or 500 ml of glucose solution).

In children, the total daily dose is 25 mg/kg/24 hours, in a glucose solution, administered in 3 infusions.

This treatment is continued for 2 to 3 days, depending on the improvement of the patient's clinical condition.

Resuscitation measures are often required at the same time :

— hydroelectrolytic reequilibration to compensate for electrolyte losses ;
— administration of glucose in order to correct hypoglycaemia induced by quinine salts ;
— antibiotics, for the treatment of possible superinfections ;
— anti-convulsives.

Often haemodialysis (filtering of the blood outside of the kidney) or even an exchange transfusion is needed, and should be performed when the hospital is equipped to do so.

When the patient's clinical state improves, parenteral treatment is relayed by oral treatment according to the schedule described above.

The treatment of visceral malaria poses a special problem. It is usually caused by Plasmodium falciparum, but may be caused by Plasmodium vivax. This type of chronic malaria responds quite satisfactorily to the prolonged administration of small doses of chloroquine : 100 mg/day for three months.

In the case of chloroquine-resistant falciparum malaria, mefloquine (LARIAM®) has been found to be effective at the dose of one 250 mg tablet a week for two months.

TREATMENT OF MALARIA IN PREGNANT WOMEN

As seen above, malaria represents a serious threat for pregnant women in malarious areas. For one thing, these women are more susceptible, particularly during the last three months of pregnancy, owing to the decrease in their natural immunological defenses. Secondly, the disease may result in prematurity, small-for-date babies and last, congenital malaria.

Episodes of malaria in pregnant women may be treated by chloroquine or even by quinine, which is not an abortive at therapeutic doses (quinine does not induce labour : it accelerates it once it has begun, but the risk of occurrence of a malarial paroxysm in the very course of delivery is practically nonexistent).

CHILDHOOD MALARIA

It should be recalled that malaria is the main cause of infantile mortality throughout the world between the ages of 1 and 5 years, and that it is the main cause of fever convulsions in subsahelian Africa.

Any rising fever suggestive of malaria should receive urgent treatment ; overmedication is preferable to insufficient treatment, since there may be an extremely rapid evolution toward severe neurological symptoms resulting in sequels and death.

The schedule should be the same as that described in the previous chapter. It should be recalled that children vomit readily, and often spit out drugs, particularly when they are bad-tasting. Making sure that drugs have actually been ingested is therefore one key to potentially successful treatment : if oral administration is too dificult, a changeover to the parenteral route should be decided.

FUTURE PROSPECTS

The only research avenues now open in the field of malaria control are the development of vaccines and of measures aimed at overcoming antimalarial drug resistance in plasmodia.

VACCINES

For many years, several research teams around the world have been working on developing a vaccine. Major breakthroughs have been made in scientists' understanding of the mechanisms of immunity to this disease, but there is still a long way to go before a vaccine can be developed for human use.

Immunization trials in animals (rodents and primates) raised great hopes at first. They made use of antibodies - anti-sporozoites, anti-gametocytes and anti-merozoites - directed against the different parasite stages.

At present, efforts are concentrating on research into Circumsporozoite Protein (CSP) : some slightly more encouraging trials have been performed on human hosts. Cell-mediated immunity has been proved to play an important role at the infected hepatocyte level, and it is therefore essential that this tissue immunity be attained.

Perhaps tomorrow's vaccine will be the fruit of the pooled achievements of these different research avenues.

OTHER AVENUES

Research projects aimed at overcoming Plasmodium falciparum resistance to chloroquine are more promising.

The in vitro adjunction of calcium-blocking agents of the verapamil (ISOPTINE®) or diltiazem (TILDIEM®) type, or of tricyclic anti-depressors to cultures of intensely chloroquine-resistant Plasmodium falciparum restores the efficacy of that drug when it is added to the culture medium : growth of the parasite is inhibited.

In vivo research is required.

The reader of this study may be tempted to adopt a pessimistic or even a completely fatalistic attitude, but he or she would be ill-advised in doing so. It is usually when faced with the most urgent situations that mankind has succeeded in discovering a new response to vital questions.

Much discussion is now focussed on malaria ; it is a topic of current importance. Talking about it helps people to learn about the disease, and it is from the information thus gathered on its epidemiology, the occurrence of resistance, new possibilities of treatment and avenues for research, that some solutions may emerge.

In endemic areas, the effects of malaria are most serious for pregnant women and children. Prolonged chemoprophylaxis for these at-risk groups is increasingly out of the question as multiple drug resistance continues to spread. It is our belief that the prevention of severe conditions requires two types of actions :

— use of mosquito-nets with or without spraying of insecticides, to limit the number of infecting bites ;
— providing health centres with means (microscopes) permitting the rapid diagnosis of high parasitaemia and the subsequent prescription of short courses of appropriate treatment.

Malaria is a serious health problem. Paradoxically, the resources allocated to malaria control activities remain terribly low, despite the extensive morbidity and mortality. Most primary health care programmes do not include malaria control measures among their priorities. Effective tools in this struggle would include reinforcement of the knowledge and action of health personnel, education programmes for schoolchildren and families, and action aimed at sensitizing planners and decision-makers to the plight of Third World countries exposed to this terrible threat.

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The situation of malaria, worldwide, gives little cause for satisfaction. the development of vector resistance to insecticides, along with population movements, socio-economic difficulties, self-medication and more or less adequate drug prescriptions all facilitate transmission of the disease and the propagation of drug-resistant strains.

The problem is further complicated when the powerlessness of families and health teams is compounded by resignation and fatalism.

In view of the alarming uspsurge of malaria, we are confident that this report, showing recent advances in the understanding of the biology of plasmodii as well as pharmacological progress, will help readers to up-date their knowledge, increase their vigilance and keep hope.

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